IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**Response Under 37 C.F.R. § 1.116 Expedited Procedure**

**In re application of:** Klinman et al.
**Application No.** 10/682,130
**Filed:** October 7, 2003
**Confirmation No.** 1348
**For:** METHOD OF TREATING INFLAMMATORY LUNG DISEASE WITH SUPPRESSORS OF CPG OLIGONUCLEOTIDES
**Examiner:** Nina Archie
**Art Unit:** 1645
**Attorney Reference No.** 4239-66902-01

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## DECLARATION OF DENNIS KLINMAN UNDER 37 C.F.R. § 1.132

1. I, Dennis Klinman, am an inventor of the above-referenced patent application.

2. It is my understanding that claims 35, 46, 47, 54 and 60-87 of the above-referenced patent application are rejected under 35 U.S.C. 112, first paragraph, as allegedly not being enabled by the specification. Specifically, the Office action alleges that the specification is only enabling for methods for reducing the production of TNFα, MIP-2, IL-6 and KC that are induced by an immunostimulatory CpG oligodeoxynucleotide (ODN), wherein the methods include the use of nucleic acid sequence set forth as SEQ ID NO: 1 (claim 35), SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination thereof. The Office action alleges that the specification is not enabling for methods for reducing the production of TNFα, MIP-2, IL-6 and KC that include only the administration of an ODN comprising nucleic acid sequence set forth as SEQ ID NO: 1 (claim 35), SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, in the absence of induction by an immunostimulatory CpG ODN. The scientific data does not support this allegation.

3. The use of an immunostimulatory CpG ODN is a common model for inflammation induced by bacterial DNA. Specifically, synthetic CpG DNA motifs mimic the immunostimulatory activity of bacterial DNA. Immunostimulatory CpG motifs directly stimulate human B cells and plasmacytoid dendritic cells, promote the production of Th1 and proinflammatory cytokines, and trigger maturation of antigen presenting cells (see Klinman et al., J. Leukocyte Biol. 84: 958-964, 2008, copy attached as Exhibit A, a brief review of the model system is provided in the abstract and the introduction on page 958). Immunostimulatory ODNs induce inflammation through the Toll-like receptor (TLR)9 receptor. Suppressive ODNs, such as SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 21 are believed to act by blocking activation of the TLR7 and/or TLR9 receptor (see Exhibit A, page 959, column 1 and Gursel et al., J. Immunol. 171: 1393-1400, 2003, copy attached as Exhibit B).

One of skill in the art readily understands that the induction of inflammation by CpG ODNs is a model system that is used to identify anti-inflammatory agents. As an example, suppressive ODN A151 (SEQ ID NO: 2) suppresses inflammation induced by CpG ODN. A151 is also effective in suppressing inflammatory arthritis induced by CpG ODN, collagen (see pages 960-961), and lipopolysaccharide (LPS, see Exhibit A, page 961). These results demonstrate that a suppressive ODN that inhibits inflammation induced by CpG ODN can also suppress inflammation induced by other agents. The ability to suppress inflammation is result of the biological mechanism of action of the suppressive ODN itself; the ability of a suppressive ODN to inhibit cytokine secretion does not result from the inducing agent.

The results demonstrate that if a suppressive ODN reduces cytokine secretion induced by immunostimulatory CpG motifs, the suppressive ODN can also reduce inflammation induced by other means.

4. H154 (SEQ ID NO: 1) has been demonstrated to reduce tumor necrosis factor (TNF)α, macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 and keratinocyte chemoattractant (KC) expression induced by CpG ODN (see the Declaration under 37 C.F.R. §

1.132 submitted on June 18, 2010). This suppressive ODN also inhibited the production of TNFα, and MIP-2 induced by bacterial DNA (see Figure 1 of Yamada et al., Crit. Care Med. 32: 2045-2049, 2004, copy attached as Exhibit C). H154 was effective at decreasing production of TNF-α, MIP-2 and IL-6 both *in vitro* and *in vivo* (see Figure 5). Thus, H154 (SEQ ID NO: 1) was demonstrated to decrease cytokine production induced by another inflammatory agent, specifically bacterial DNA. This provides evidence that, using guidance provided by the specification, one of skill in the art could use H154 to reduce cytokine production induced by means other than an immunostimulatory CpG ODN.

As suppressive ODNs act through a common biological mechanism, an ODN including the nucleic acid sequence set forth as SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20 also will decrease production of TNF-α, MIP-2, IL-6 and KC induced by other means, such as, but not limited to, bacterial DNA.

5. All statements made herein and of my own knowledge are true and all statements made on information are believed to be true; and further, these statements were made with the knowledge that willful false statements and like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements made may jeopardize the validity of the application or any patent issuing thereon.

Date Dec 6, 2010

Dennis Klinman, M.D., Ph.D.

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